REMARKS

The Written Description Rejection Should be Withdrawn

The Office Action of 28 July 2008 rejected claim 22 because the specification allegedly fails the written description with respect to the limitation "wherein the composition is suitable for intravenous administration." Applicants respectfully disagree. The application fully supports the concept that the adenoviral vectors of claim 22 can be injected intravenously, or "i.v." For example, support for i.v. injection can be found in at least paragraphs 0023 and 0024 of the published application (U.S. Pregrant Publication No. 2004/0156827). Specifically, paragraph 0023 of the published application states that adenoviruses "infect a great variety of cells, however, when they are administered *i.v.*, most of them are located in the hepatic organ … ." Moreover, paragraph 0102 of the published application states that "[t]he results of the present invention show that the injection of $3x10^{11}$ viral particles by iliac vein in normal Wistar rats of approximately 200 g. produces a very high level of expression (70% of transduced hepatocytes)" (emphasis added).

Applicants assert that the specification fully supports claim 22 as written. Applicants respectfully request reconsideration and withdrawal of the written description rejection.

The Enablement Rejection Should be Withdrawn

As an initial matter, Applicants point out that the Office Action is internally inconsistent. It is not permissible to, on one hand, assert in the enablement rejection that, no one could read the present specification and make and use the claimed invention, while on the other hand, in the obviousness rejection, assert that anyone could have read the art and made the currently claimed invention. Such inconsistency is precisely what has happened here.

The Office Action of 28 July 2008 rejected claims 22, 24, 28-30 and 32-34, because the specification allegedly fails to enable "a pharmaceutical composition comprising recombinant

adenovirus expressing the proteins as recited in the claims under the control of various promoters ... ." *Office Action,* page 3. Applicants respectfully disagree.

Applicants note that the test for enablement is whether one of skill in the art would have to perform undue experimentation to practice the claimed invention. *See In re Wands,* 858 F.2d. 731 (Fed. Cir. 1988). Applicants have provided a blueprint for making and using various embodiments of the claimed invention in Example 2 of the present application. Example 2 discloses the use of MMP-8 protein as a therapeutic. The adenovirus can be injected intravenously and the injection of the adenovirus results in high expression levels of protein (see paragraph 0102). Applicants assert that the application provides more than ample guidance for making an injectable adenovirus for treating liver fibrosis.

The proteins listed in the claims (MMP-8, 1, 2, 9, 13 and a truncated TGFβII receptor) are known in the art to be useful for collagen degradation. Thus, the state of the art at the time of filing can be relied upon for showing that MMPs and a truncated TGFβII receptor are useful for collagen degradation, which, in turn, can be useful for treating fibrosis.

The entire enablement rejection appears to be premised on the position that "[t]here is no evidence of record that the claimed adenoviral vector expressing the recited therapeutic protein of combination of therapeutic proteins would be able to provide therapeutic effect *in vivo* so as to treat hepatic fibrotic disease or disorders." *Office Action*, page 5 (emphasis added). Such a basis for an enablement rejection, however, is entirely inappropriate. Indeed, the MPEP clearly states that "lack of working examples or lack of evidence that the claimed invention works as described should never be the sole reason for rejecting the claims invention on the grounds of lack of enablement." MPEP §2164.02 (emphasis added).

Applicants also provide herewith copies of journal articles that demonstrate that viability of the claimed invention. The submitted journal articles, some of the authors of which overlap with Applicants, were published after the priority date of the present invention; thus the articles

do not qualify as prior art to the claimed invention. The submitted articles, however, represent post-filing data showing that one of skill in the art could read the present specification and make and use the claimed invention. Applicants assert that the specification fully shows one of skill in the art how to make and use the claimed invention as evidenced by the post-filing data in the submitted articles.

When examined in light of "the Wands factors" for assessing enablement (MPEP §2164.01(a)), and in view of the post-filing data demonstrating successful reproduction of the claimed invention, the inescapable conclusion is that the specification fully informs one how to make and use the claimed invention. Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

The Obviousness Rejections Should Rejections Should be Withdrawn

Fernandez and Hasty

The Office Action of 28 July 2008 rejected claims 22 and 28 as allegedly obvious in view of Fernandez (*Surgery*, 124:129-136 (1998)) and Hasty (*JBC*, 265(20):11421-11424 (1990)). Applicants respectfully disagree.

As an initial matter, Applicants point out that the Office Action is internally inconsistent. It is not permissible to, on one hand, assert in the enablement rejection that, no one could read the present specification and make and use the claimed invention of claims 22 and 28, while on the other hand, in the obviousness rejection, assert that anyone could have read the art and made the currently claimed invention of claims 22 and 28. Such inconsistency is precisely what has happened here.

In making the enablement rejection, the Office Action examines the phrase "to treat liver fibrosis" as a limitation and states that "[t]here is no evidence of record that the claimed adenoviral vector expressing the recited therapeutic protein of combination of therapeutic proteins would be able to provide therapeutic effect *in vivo* so as to treat hepatic fibrotic disease

or disorders." *Office Action*, page 5. In making the obviousness rejection, the Office Action states that "[w]hether the claimed composition is used for intravenous administration to treat liver fibrosis is irrelevant to the claimed composition." *Office Action,* pages 6-7. Thus it appears that the Office Action is using the phrase "to treat liver fibrosis" as a limitation when examining the application for enablement purposes, but that the Office Action is disregarding this phrase as a limitation when examining for obviousness purposes. Applicants fully recognize that the Office is given great deference for claim interpretation and that claims must be interpreted as broadly as is reasonably possible during examination. But Applicants submit that the Examiner's claim interpretation must remain internally consistent. Applicants respectfully request that the Office clearly define which phrases are being treated as limitations and which phrases are not being treated limitations so that adequate responses to the Office Action may be provided.

Turning to the substance of the rejection, the Office Action states that "serotype Ad5 and deletion of E1 region … are well known in the art and are obvious to one of ordinary skill in the art at the time of the invention." *Office Action,* page 7. The Office Action, however, fails to cite to any references that teach these limitations. The combination of cited references therefore fails to recite each and every element of the claimed invention. Accordingly, the combination of references must necessarily fail to establish a *prima facie* case of obviousness against the claims 22 and 28.

Moreover, Fernandez does not teach intravenous administration of an adenovirus. Rather, Fernandez discloses an *ex vivo* experiment where veins were removed from patients and incubated with adenovirus particles. Hasty does not cure this deficiency, as Hasty is cited merely for the MMP-8 cDNA sequence. Moreover, Fernandez states that "adenovirus-mediated gene delivery is limited to the vessel's intima" and makes no mention of systemic administration, such as intravenous administration, of adenovirus particles.

It is well established that, to establish a *prima facie* case of obviousness, there must be a reasonable expectation of success and that this expectation must be grounded in the prior art. *See*

In re Vaeck 947 F.2d 488, 493 (Fed. Cir. 1991). Based on the Office Action's own admissions, one of skill in the art could take no guidance from Fernandez and/or Hasty to arrive at the claimed invention with any reasonable expectation of success. Indeed, in putting forth the enablement rejection, the Office Action states "MMP-1, 2, 8, 9, 13 ... are different proteins and having diverse biological functions. Even MMP-8 proteins from different organisms could have different biological functions." *Office Action,* page 4. If this were true on page 4 of the Office Action, why would it be a mere matter of substituting MMP-8 for MMP-3 in the obviousness rejection, just 2 pages later? Based upon the Office Action's own admissions, therefore, one of skill in the art would have no reasonable expectation of success in substituting MMP-8 for MMP-3. Applicants submit that the references, alone or in combination, fail to establish a reasonable expectation of success in generating the products and methods of the present invention, since the references fail to even mention intravenous administration.

Thus, the references fail to establish a *prima facie* case of obviousness. The references fail to teach each and every element of the claimed invention and the references fail to instill any expectation of success to one of skill in the art. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

Baker

The Office Action of 28 July 2008 rejected claims 22 and 33 as allegedly obvious in view of Baker (*Matrix Biology*, 15:383-395 (1996)). Applicants respectfully disagree.

As an initial matter, Applicants point out that the Office Action is internally inconsistent. It is not permissible to, on one hand, assert in the enablement rejection that, no one could read the present specification and make and use the claimed invention of claims 22 and 33, while on the other hand, in the obviousness rejection, assert that anyone could have read the art and made the currently claimed invention of claims 22 and 33. Such inconsistency is precisely what has happened here.

In making the enablement rejection, the Office Action examines the phrase "to treat liver fibrosis" as a limitation and states that "[t]here is no evidence of record that the claimed adenoviral vector expressing the recited therapeutic protein of combination of therapeutic proteins would be able to provide therapeutic effect *in vivo* so as to treat hepatic fibrotic disease or disorders." *Office Action*, page 5. In making the obviousness rejection, the Office Action states that "[w]hether the claimed composition is used for intravenous administration to treat liver fibrosis is irrelevant to the claimed composition." *Office Action,* pages 7. Thus it appears that the Office Action is using the phrase "to treat liver fibrosis" as a limitation when examining the application for enablement purposes, but that the Office Action is disregarding this phrase as a limitation when examining for obviousness purposes. Applicants fully recognize that the Office is given great deference for claim interpretation and that claims must be interpreted as broadly as is reasonably possible during examination. But Applicants submit that the Examiner's claim interpretation must remain internally consistent. Applicants respectfully request that the Office clearly define which phrases are being treated as limitations and which phrases are not being treated limitations so that adequate responses to the Office Action may be provided.

Turning to the substance of the rejection, Baker does not teach intravenous administration of an adenovirus. Rather, Baker discloses an *in vitro* experiment where adenovirus particles were co-cultured with MCF-7 (adenocarcinoma), SMC (smooth muscle cells) HEK293 (human embryonic kidney) cells. Moreover, Baker makes no mention of systemic administration, such as intravenous administration, of adenovirus particles.

Thus, one of skill in the art could take no guidance from Baker to arrive at the claimed invention. It is well established that, to establish a *prima facie* case of obviousness, there must be a reasonable expectation of success and that this expectation must be grounded in the prior art. See *In re Vaeck* 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants submit that the reference, alone or in combination, fails to establish a reasonable expectation of success in generating the products and methods of the present invention, since the reference fails to even mention

intravenous administration. Applicants respectfully request reconsideration and withdrawal of the obviousness rejection.

The Claimed Invention Is Patentable

Further bolstering Applicants' arguments as to the patentability of the claimed methods, Applicants point to EP Patent No. EP 1221490, JP Patent No. JP4173663, MX Patent No. 252920, CA Patent No. 2,385,538, AR Patent No. AR 025692, HK Patent No. 1049860 which are some of the foreign counterpart to the present application, all of which claim priority to PCT/MX00/00035, as does the present application. While Applicants recognize that these examination authorities have no authority over the USPTO, Applicants nonetheless point out that these examination authorities, with similar standards regarding obviousness/inventive step, found such methods claims patentable. Accordingly, Applicants respectfully request reconsideration and withdrawal of the enablement and obviousness rejections.

CONCLUSION

Applicants have amended the claims to better capture the envisioned commercial embodiments. In addition, Applicants have presented responses to the Office Action regarding the patentability of the presently claims.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

Date 28 October 2005 By _____

MORGAN LEWIS & BOCKIUS LLP
Customer Number: 09629
Telephone: (202) 739-3000
Facsimile: (202) 739-3001

Todd B. Buck
Registration No. 48,574